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# OTOSCLEROSIS STUDY GROUP

**October 8, 1949**

GEORGE E. SHAMBAUGH, JR., M.D., *President*

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# THE FISSULAR REGION OF THE OTIC CAPSULE IN RELATION TO OTOSCLEROSIS

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IN an investigation based on an examination of more than 300 series of sections covering specimens from the 6-mm. embryo to the 70-year adult, the development of the temporal bone and its adult histologic structure have been studied with particular reference to pathologic changes in the fissular region of the otic capsule.

In this discussion, which must be brief, the author will account for the development of the fissula and of the neighboring portions of the otic capsule, the normal adult structure of the same regions, and those pathologic alterations which occur in and around the fissula which result in one form of deafness.*

The adult temporal bone is "petrous" only where it serves as a bed for the membranous labyrinth. The petrous part is only that portion which houses the otic labyrinth. Marrow and air spaces occupy much of the remainder. They are late fetal additions to the primordial otic capsule.

Despite its relative density, the capsule is crossed by four fissures of perilymphatic nature, namely, the vestibular and cochlear aqueducts, the fossula post fenestram and the fissula ante fenestram. From the present standpoint the most important of these is the fissula, named for its position anterior to the vestibular (oval) window. The fissula is consequential because it lies at the core of the so-called "site of predilection" of otosclerosis.

The fissula ante fenestram begins externally on the medial wall of the tympanic cavity. It ends internally at the junction of the vestibule and the scala vestibuli. The fissula is a constant anatomic feature. Although typically it is filled with a moderately vascular fibrous tissue, it is sometimes occupied by a large mass of cartilage, or by bone of sclerotic type. For this reason the morphogenesis of the fissular region is worthy of detailed study.

## DEVELOPMENT AND NORMAL STRUCTURE OF THE FISSULA ANTE FENESTRAM

The fissula makes its appearance in the fetus of 9 weeks (34 mm.) as an anteriorly directed outpushing of the periotic connective tissue of the vestibule. In the fetus of 10 weeks (50 mm.) there occurs a dissolution of that portion of the precartilage of the primitive capsule which immediately surrounds the periotic projection—in just the way that the same tissue is removed to permit enlargement of any part of the otic labyrinth. Cartilage is formed, then locally destroyed. The fissula gradually widens and lengthens, reaching the opposite, or tympanic, surface of the capsule in the fetus of 13 weeks (75 mm.). The process of burrowing requires five weeks, and the fissular tract is distinct

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* Detailed, illustrated accounts of the observations reported herein have already appeared in the Annals of Otology, Rhinology and Laryngology, 56:957-985 (Dec.) 1947; 57:103-128 (March); 603-632 (Sept.) 1948.

in the 14-week (100-mm.) fetus. In this way a perilymphatic channel is produced, complete from the inner to the middle ear.

By the fifth month of prenatal life (in the fetus of 21 weeks, or 183 mm.) the fissula has attained maximum normal size. Concurrently, the cochlea, the vestibule, the semicircular ducts, the otic capsule and the ossicles also reach full adult dimensions. The remaining prenatal months and all the years of infancy, childhood and manhood are available, so to speak, for histologic maturation or for genesis of pathologic tissue.

At this stage (midterm fetus) the cartilage of the primordial capsule remains as a tube within which is lodged the fibrous tissue derived from the original periotic extension. This cartilage is continuous with a chondral rim bordering the vestibular window. This continuity is maintained even in advanced age. At the tympanic extremity of the fissula there is similar continuity—later to be interrupted. Perichondral bone now covers the capsule. Between this platelike bone on the periphery and the cartilage enclosing the fissula, at the core of the capsule, osseous tissue of an unusual type is being formed through rapid calcification and ossification. This converted cartilage is intrachondral bone, composed of so-called cartilage islands.

The cartilage has been almost completely removed by the 23-week (210-mm.) stage. It is represented only by a thin chondral or perichondral layer. This pellicle lines the newly formed bone which has spread to form an uninterrupted wall for the fissula. The fibrous content remains unchanged.

In mature form the fissula passes inward from a lateral orifice, which opens on the submucosal tissue of the tympanic cavity. Turning at a right angle, toward the vestibular window and away from the cochlea, the fissular tract descends as it passes to an opposite medial orifice. This medial inner orifice opens on the periotic tissue of the vestibule. The cartilage which lines the wall of the vestibule remains continuous with that of the fenestra; usually in the adult, it does not reach the tympanic orifice. Usually the fissula approaches, but does not terminate in, the vestibular window.

In some specimens an auxiliary, or fenestral, opening occurs (as may be found in specimens from all age groups). In such instances the connective tissue of the fissula is directly continuous with the annular ligament of the stapes; or, in terms of space rather than content, the fissula opens into the vestibular window. When present, the fenestral opening is established in the fetus; it appears as a deep oblique cleft in the capsular wall, and extends without interruption from the wall of the vestibule upward and outward, across the rim of the vestibular window to the tympanic cavity. Now, were the cartilage lining of the fissula to undergo new growth, its spreading tissue could invade the vestibular window by way of a channel ready-made. Therefore, to cause a deforming pathologic process, there is merely required chondromatous growth, or the latter replaced by sclerotic bone.

### PATHOLOGIC CONTENTS OF THE FISSULA

The "space" of the fissula, that is, the capsular fault occupied normally by connective tissue, possesses typically the form of the letter *C*. Usually it is compressed, to appear bladelike; in some instances the fissula extends upward (that is, cranialward) beyond the level of the tympanic orifice; not infrequently the fissula is capacious throughout its entire length.

A large fissular tract seemingly invites histologic activity. Cartilage, produced by the normally quiescent peri-

chondrium of the fissular rim, may come to occupy part, or it may obliterate all, of the enlarged fissula ante fenestram—as if the latter were a structural defect.

In anticipation of conclusions based on observations next to be presented, it may be said that, although otosclerotic bone has been found in various portions of the otic capsule, the commonest site of occurrence is the region of the fissula ante fenestram. This is the area, too, where masses of abnormal cartilage, or chondromas, are most frequently seen. Of course, simple masses of residual cartilage occur elsewhere in the otic capsule; they, however, disappear at the time of birth or during early postnatal years. These transitory nodules or seams are found at the base of the styloid process, at the petrosquamous suture, at the subarcuate fossa, around the inferior margin of the cochlear (round) window and near the internal acoustic meatus.

It is only in the fissular region that cartilage is formed anew, postnatally, to encroach on a space which in most instances (that is, normally) remains filled with connective tissue. In the fissula the abnormal mass develops from the chondral rim, already described, which intervenes between the fissular connective tissue and the surrounding shell of bone. This new cartilage is histologically different from that of the parent tissue; depending on the stage encountered, it is either actively spreading or is preparing to undergo initial ossification. In almost every instance the cartilage occurs in a fissula which is unusually large—as if it were reducing the size of the fissular cleft in the bone. Such a chondroma may occupy either end of the fissula, the fenestral orifice which opens into the stapedial joint, the cupola-like space which sometimes occurs cranial to the level of the tympanic opening, or even the entire space of the fissula.

Regularly, the margin of such a chondral mass slowly undergoes ossification, bone replacing cartilage by a familiar series of steps to form a gnarly lump. Sometimes the process does not stop when an osseous nodule has been produced; rebuilding continues, further excavation being accompanied by new deposition, with resultant obliteration of not only the fissular connective tissue but also of the quiescent cartilage of the original fissular rim and the surrounding endochondral and intrachondral bone of the otic capsule. In advanced stages, the otosclerotic bone reaches the vestibular window and takes the place of the normal tissue. This is the terminal stage usually described in the literature.

Putting these circumstances together in a series of developmental steps, it seems that the natural sequence is as follows: (1) closure, partial or entire, of a large (atypical) fissula by fetal or infantile growth of cartilage—the latter tissue derived from the perichondral layer which always borders the chondral rim of the fissular tract; (2) gradual osseous replacement of the chondroma, a process which in some cases continues to a pathologic degree, replacing the normal tissues of the entire fissular region with sclerotic bone.

## CONCLUSIONS

*Factual.* In the antefenestral region of the otic capsule, that is, in the area between the vestibular window and the cochlea, the structure is exceptional in being crossed by a channel (termed the fissula ante fenestram).

The fissula is formed through invasion of the primordial cartilaginous capsule by a tongue of periotic tissue; maturing, the latter becomes the connective tissue which regularly occupies the fissular tract of the adult ear.

During the process of ossification of the capsule, cartilage persists as the lining of the fissula, external to which, as early as the midterm stage, bone forms a completely investing osseous shell.

Typically, the fissular channel is C-shaped in outline, is narrow or cleftlike, and is occupied by connective tissue.

Frequently in the advanced fetus, in the infant and in the child, the fissula is capacious, the space being cylindrical rather than bladelike. In such instances a cartilage mass, or chondroma, almost invariably occupies part or all of the fissula; in some instances it remains confined to the enlarged cranial part; in others it occupies the entire fissular tract. The chondroma may reach the stapes directly when an auxiliary (fenestral) orifice occurs.

This neoplastic cartilage is derived from the persistent chondral lining of the fissula.

Usually the chondromatous mass is gradually reduced by being converted, from the periphery, into intrachondral bone. In relatively rare instances, however, the replacement is rapid and is carried out through the production of a vascular, sclerotic type of osseous tissue. Being invasive, this new, vascular bone displaces normal surrounding tissue to form part of the rim of the vestibular window and, as a consequence, to impinge on the base of the stapes.

In no other portion of the otic capsule is there encountered like evidence of histologic instability—a circumstance which renders the fissular region subject to pathologic change, the vestibular window vulnerable to invasion, and the stapes subject to fixation within its fenestra.

*Hypothetical.* It would appear that the activity by which cartilage is produced within the fissula represents an attempt to close an abnormally large cleft in the antefenestral area of the otic capsule.

It would seem, further, that the ultimate formation of sclerotic bone is a natural second step in the same process. Having been formed, the vascular bone spreads beyond the area of the original capsular defect.

# THE INCIDENCE, LOCATION AND EXTENT OF OTOSCLEROTIC LESIONS

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OTOSCLEROSIS is not a rare disease in Caucasians. Nothing is known about its incidence in the yellow races of mankind or in any of the undiluted black races. In the American Negro otosclerosis occurs much less frequently than it does in the white population of this country. The disease, so far as is known, does not occur in any species except Homo sapiens.

Otosclerosis is primarily a disease of bone; the effect of the disease on hearing is secondary to the location and extent of the bony lesion.[5,8,9] If the figures that I reported to this Study Group at its 1943 meeting[8] hold essentially true as larger collections of material are prepared and studied, approximately one-eighth of all white women, including girls 5 years of age and older, have otosclerotic lesions, and about one-fifteenth of all white males of the corresponding age group have such lesions. The incidence of clinical otosclerosis is far below that of the histologic, because in about seven-eighths of the ears that have otosclerotic lesions the condition gives rise to no symptoms, and the presence of the disease is never suspected unless serial histologic sections of the temporal bones are made and studied with a microscope. Only in about one-eighth of the ears that have histologically demonstrable otosclerosis is the location and the extent of the osseous lesion such that impaired hearing results. There may be occasional exceptions, but in general otosclerosis does not affect hearing acuity until or unless ankylosis of the stapediovestibular articulation occurs. In other words, to cause impaired hearing an otosclerotic lesion must invade, and replace with its peculiar kind of new bone, some portion of the articular cartilage and the adjacent part of the annular ligament. The mere presence of an otosclerotic lesion near or in contact with the annular ligament does not interfere with the transmission of air-borne sound to the inner ear; to do so it is necessary that an osseous bridge, or connection, be established between the oval window margin and the stapedial footplate. The bridge may be narrow, but it must exist before hearing acuity is affected by an otosclerotic lesion. Rarely, if ever, is the entire annular ligament obliterated and replaced by the otosclerotic osseous tissue; I personally have not seen any case in which the annular ligament was not still present at some part of the circumference of the joint.

The invasion and replacement of the annular ligament usually occurs from

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In the presentation of this paper at the symposium, 11 lantern slides were used to illustrate points discussed. Each was a photomicrograph of a histologic section of a human ear that had otosclerosis. All of the photomicrographs have previously been published, either in the author's paper on Histologic Otosclerosis (Ann. Otol., Rhin. & Laryng., 53:246-266 [June] 1944) or in his paper on Early Stages of Otosclerosis (Arch. Otolaryng., 12:457-483 [Oct.] 1929). Because these sources are readily available to most readers, republication of the illustrations, which would occupy as much journal space as does the text matter, does not seem justified and has not been requested.

the side of the oval window margin, but it may take place in the other direction. In those cases in which the otosclerotic process begins in the stapedial footplate, the direction of the invasion, if ankylosis occurs, must be from the footplate towards the oval window margin. This direction of spread of a diseased area is also possible, and does occur sometimes, in the formation of secondary bony bridges in ears in which an otosclerotic area primary in the otic capsule has invaded the stapedial footplate and spread through its substance. Histologic demonstration that the direction of spread of otosclerosis in an ear was really from the stapedial footplate to the oval window margin will always be difficult, in either type of case, because once the "bridgehead" in the oval window margin has been established, uncertainty exists about the direction in which the extension actually occurred. For this reason, in the report I made six years ago only 10 ears were listed as having an otosclerotic area primary in the stapedial footplate; each of them had an area definitely limited to that structure at the time of death.[8] In the recent report made by Bengt Nylén,[9] based on his study of Nager's collection of sectioned ears, 2 similar cases are mentioned, and I understand that Fowler[6] and perhaps others have a few such specimens. The fact that otosclerosis can spread from the stapes to the oval window margin, as well as in the usual direction, may be of only academic interest. I am stressing it this evening, however, for two reasons: (1) because neither the possibility nor its clinical implications have been given serious consideration in the extensive literature on otosclerosis; and (2) because the footplate of the stapes, unlike the crura or either of the other two ossicles, is throughout its development in close contact with the primordial otic capsule. The meticulous studies of Anson, Bast and Cauldwell[2,3,4] have conclusively settled the long discussion about the role of the otic capsule in the embryology of the stapes, and the developmental facts they have demonstrated may, if the ultimate cause of otosclerosis ever is ascertained, offer a rational explanation of the occurrence of the disease in the stapedial footplate.

Otosclerotic areas differ in size, from ones less than a millimeter in diameter to ones in which the disease process has involved almost the entire otic capsule. Small and moderate sized areas occur far more often than do the truly extensive ones.

Usually only one otosclerotic area is present in a temporal bone, but two anatomically separate areas occur rather often, and three or more independent areas develop occasionally in an ear. For the material reported to you six years ago, the actual figures were: 54 ears had one area each, 22 ears had two areas each, and 5 ears had three areas each; the total number of otosclerotic areas in the 81 ears was 113. Nylén[9] reported that one of the specimens he studied had four independent otosclerotic foci.

The disease process may begin in almost any portion of the otic capsule. More than half of all otosclerotic areas arise in the region immediately in front of the oval window, and over three-fourths of all ears that have histologically demonstrable otosclerosis have this region involved. Obviously there is good reason for calling it the "area of predilection" for otosclerosis.

In his part of this evening's symposium Dr. Anson,[1] after describing in detail the development of the region of the otic capsule immediately anterior to the oval window, expressed the opinion that the cause of otosclerosis is related to the changes that occur in the tissues of the peculiar structure known as the

fissula ante fenestram. From previous friendly discussions we have had on the subject during the past twenty years or so, both Dr. Anson and Dr. Bast are well aware that on this point I do not agree with them. Two facts constitute the principal reasons for my disagreement with their otherwise plausible hypothesis about the origin of otosclerosis. The two facts are: (1) that otosclerosis, histologically indistinguishable from that which occurs in the area of predilection, can and often does originate in parts of the otic capsule far removed from the fissula ante fenestram; and (2) that at least some of the otosclerotic areas anterior to the oval window, when still of small size, are not in contact with any portion of the fissula ante fenestram. The collection of sectioned temporal bones at Hopkins contains four such specimens.[7,8] After an otosclerotic area anterior to the oval window has grown even to moderate size, it is quite impossible to determine, from the study of histologic preparations, whether or not the area originated independently of the fissula ante fenestram, because this structure has by then been replaced by the new growth.

The round window region ranks next to the oval window in the frequency with which otosclerotic lesions develop; about one-fifth of all histologically recognized areas of otosclerosis are somewhere along the zone of attachment of the round window membrane.[8] Only rarely do areas in this region develop into major lesions, i.e., into ones that occlude the round window niche or that might otherwise affect the acuity of hearing. Likewise, the lesions in the regions of less frequent occurrence of independent development of otosclerosis seldom, if ever, grow to a size such that they, by their presence, affect the hearing. This is true for the independent areas in the superior, the anterior, or the inferior parts of the cochlear capsule, in the part of the capsule around the semicircular canals, or in the inferior part of the wall of the internal auditory canal.

Reflection upon the facts that have been revealed by histologic studies of otosclerosis naturally leads to curiosity about why the disease usually is innocuous. Thoughtful persons ask themselves why it is that most otosclerotic areas stop growing before they involve structures essential to the hearing function and whether the answer to this question, if known, might prove useful in the development of a rational method to stop the growth of all otosclerotic areas and thus prevent the progressive spread of those areas that cause the symptoms of clinical otosclerosis. Nutritional factors, using the term nutrition in the broadest sense, are known to be important in the control of growth in general, therefore thoughts about the growth of otosclerotic areas have naturally turned to a consideration of items that might affect the nutritional environment of the tissues of the otic capsule. I shall not attempt at this time to review or to summarize the studies that have been made by others along this line, except to remark that thus far they have not been successful in revealing what controls either the onset or the growth and spread of otosclerotic areas. I do wish, however, to mention two morphologic facts that are of interest and that should be given consideration in thinking about the possible role of nutritional factors in otosclerosis. The first fact is that otosclerosis occurs unilaterally. In the material I have studied, about 30 per cent of the individuals who had histologic otosclerosis had only one ear involved; Nylén found a similar proportion, "somewhat over 25 per cent," of unilateral cases in the material he studied. The second fact, which is the more important one from the stand-

point of the growth as distinct from the pathogenesis of otosclerotic areas, is that in individuals who have bilateral otoscelerosis, bilateral symmetry of the areas is not always present. Not only may the otosclerotic areas in the two ears of a person differ in location and extent, but similarly located areas may differ from each other greatly with respect to the stage of activity present. The histologic appearance of the sectioned area in one ear may, for instance, afford good evidence that it was growing actively during the period immediately preceding death, while the appearance of the otosclerotic area in the other ear is that of complete quiescence for a long time. Attempts to explain the pathogenesis of otosclerosis and the growth of otosclerotic areas after their inception should take into account the above morphologic facts, unilateral occurrence of the disease and bilateral differences in growth activity of diseased areas, together with the physiologic fact that, in any individual, the blood has supplied both otic capsule with the same nutritional factors for identical length of time, irrespective of temporary or permanent deviations of any of the factors from the range of normal.

Despite all that has been learned about otosclerosis, its basic riddle remains unsolved.

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# OTOSCLEROSIS: HYPOTHESIS OF ITS ORIGIN AND PROGRESS

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THE difficulty in giving a precise characterization of the histopathology of otosclerosis has long been recognized. And yet the microscopic picture is clear-cut and easily identified. How can such a paradox be?

We have inherited from men of great integrity, who had a wealth of clinical and microscopic experience, what might be called a multiple picture of otosclerosis. What is the significance of this fact?

The architectonic structure of haversian systems in the normal otic capsule is very complicated. Because of the irregular shape of the capsule, the blood vessels supplying it are forced to make rapid and complicated curves in their course through it. Consequently, in every microscopic section we get a variety of patterns of bony lamellas. Occasionally, haversian canals will be cut at right angles to the long axis of the vessel, giving the textbook picture of a haversian system. More often they will be cut at various tangents, giving an intricate and irregular pattern of lamellas. In certain areas the lamellas, and even the vessels themselves, will be cut in longitudinal plane (fig. 1).

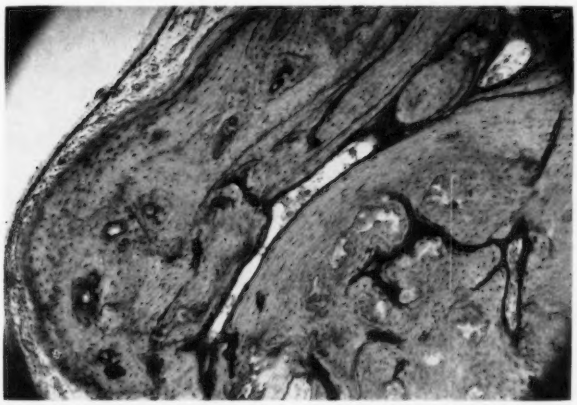

FIG. 1—The intricate and irregular architectonic structure of haversian systems in the normal otic capsule of the adult. Interspersed among the globuli interossei are blue mantles. Lamellas may appear in concentric formation or in linear formation, according to the angle of cutting.

With the intricacies of the normal anatomy in mind, let us discuss the pathologic picture present in otosclerosis.

The otosclerotic lesion presents a circumscribed area of spongy pathologic bone

From the Lempert Institute of Otology.

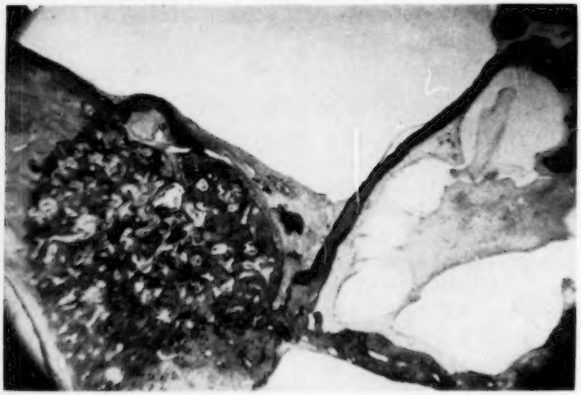

FIG. 2—A typical case of otosclerosis. The lesion lies anterior to the footplate of the stapes. Ankylosis has occurred. The footplate is also involved. The pathologic bone is pitted with vascular and fibrotic spaces. The contour of the lesion presents a scalloped appearance because the disease advances by haversian systems. Attack upon the next haversian canal is evident in the upper left field. The case was bilateral. (Washington University Collection. Courtesy of Williams & Wilkins.)

FIG. 3—An otosclerotic lesion involving the round window. Oval window was not involved. A fracture line occurred between the niche of the round window and the ampulla of the posterior canal, as shown in figure 11. White male, 21 yrs. (Washington University Collection, 7010.)

clearly demarcated from the normal bone. The contour of the diseased area is usually more or less scalloped, following the pattern of haversian systems. The disease is definitely seen to advance along blood channels. Congestion and stasis are a common observation, as Wittmaack[15] noted.

The most common site of occurrence is in the region of the oval window (fig. 2), but it may occur in the round window (fig. 3). It may also occur between the two windows (fig. 4), in the internal audi-

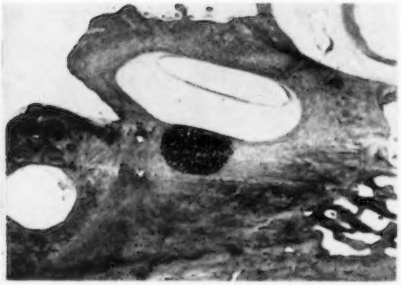

FIG. 4—An otosclerotic lesion medial to the basal turn of the cochlea, near neither window. In this location no known clinical symptoms can be elicited. White male, 46 yrs. (Washington University Collection, 8630.)

tory meatus, near the apex of the cochlea, near the superior semicircular canal, or in the external auditory canal.

It may involve the region of the fissula ante fenestram, as discussed by Bast, by Anson and by Guggenheim (fig. 5). Although usually circumscribed it may be diffuse (figs. 6, 7, 8).

The blood vessels in otosclerotic cases, as seen under the microscope, exhibit blue mantles. These were described by Manasse.[8] It was recognized by Manasse and Nager[11] that resorption of bone along these blue mantles could occur without the aid of osteoclasts. Nylén,[13] on the other hand, writing in 1949, does not believe blue mantles are significant because "they occur around semicircular canals where the disease is rarely seen."

I believe that blue mantles may be considered as chemical indicators, so to speak, of the type of calcium being deposited or existing along the course of a vessel. Blue mantles are observed in temporal bones that are not otosclerotic, but they are a prominent characteristic of otosclerosis. The spread of the pathologic fluid from the blood stream can be traced through the canaliculi to the adjacent lacunas, giving the appearance of insects walking along a stick (fig. 9). At a later stage the evidence of its presence can be traced along the canaliculi on the other side of these lacunas to those not in immediate contact with a haversian canal.

Osteoclasts may be present in such great numbers that osteoclasia has been considered as a diagnosis.

Moritz Weber[14] and others stressed the braided bone that appears in otosclerosis, the so-called *breccia.* Figure 10 illustrates a haversian canal in an otosclerotic center of bone. We can see the somewhat shriveled endothelial cells on the wall of the vessel. Increased permeability allows the detrimental fluid to pass through. Evidence

FIG. 5—Otosclerosis may involve the region of the fissula ante fenestram. (Washington University Collection, 5178.)

FIG. 6—A diffuse type of otosclerosis involving the inferior border of the facial canal, the oval window, promontory, round window and the border of the posterior ampulla. (Dr. Lempert's case, S.L.)

of a widening or decalcification of the bony canal is seen below center. Here also we see parallel bands interlacing each other. At this stage they are mere shadows of old cement lines. At a later stage, when repair has set in, they will present the picture illustrated in a recent report on ossicles in otosclerosis by Dr. Lempert and myself.[7] There you saw dense fiber bone with loss of normal haversian system contours and an enlargement of lacunas. This structure shows up very well in unstained sections when examined in polarized light, as was done by Weber.

Sometimes the disease definitely assumes the characteristics of a tumor of the bone. Otto Mayer,[9] observing this fact, concluded that it was a vascular tumor. He called it a hematroma. But Mayer thought that it arose from the attempt on the part of Nature to heal a fracture of the otic capsule. To him it was something like a callus. In our small collection of cases we have three examples of fracture lines. None of these occur through the pathologic bone. We are forced to conclude that the fractures occur because of the disease. The

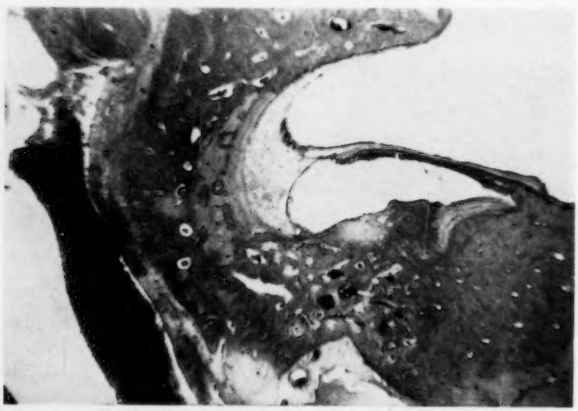

FIG. 7—Involvement of the promontory and niche of round window. Obliteration of membrana tympani secundaria with protrusion of atypical bone into scala tympani. Note that the attack on the inner bony promontory wall is around blood vessels. White female, 47 yrs. (Dr. Lempert's case, S. L.)

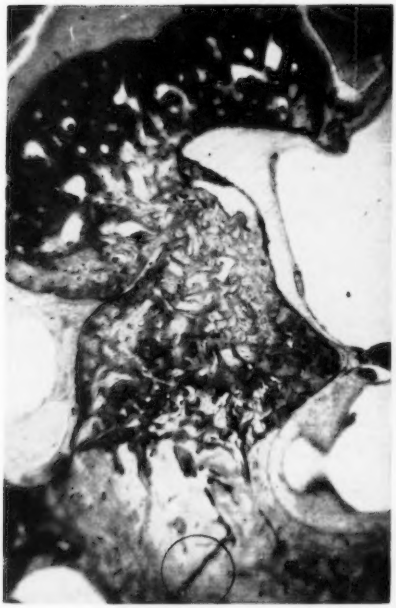

FIG. 8—Osteoporotic changes are seen in the upper field. Hypervascularity, congestion, stasis and fibrosis appear in the central field. Inferiorly, the pathologic extension occurs along vascular channels. (Dr. Lempert's case, S.L.)

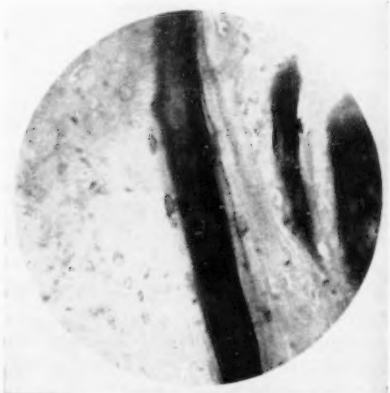

FIG. 9—Microscopic evidence of extension of pathologic chemical fluid from blue-mantled haversian canals through canaliculi to adjacent lacunas. This gives the appearance of insects walking along a stick. The neighboring lacunas are devoid of bone cells, indicating necrosis. (Detail from fig. 8.)

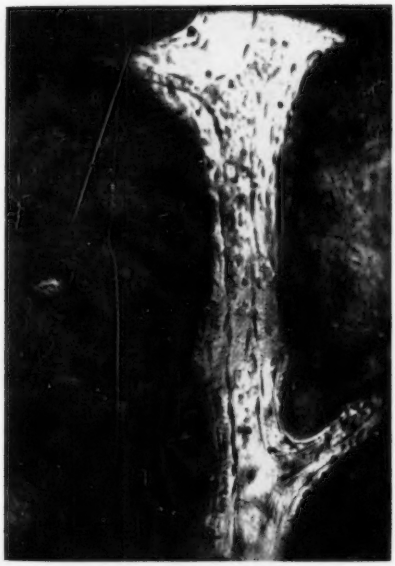

FIG. 10—Longitudinal section of a haversian canal passing through otosclerotic bone. Note the shadowy braided structure at an expanded region just below the center of the field, the "breccia" or braided bone. Note also the endothelial cell with crenulated cytoplasm in the lower portion of the field.

spongification of the bone has altered the normal architectural bulwark of the petrosa as a support to the dome of the skull and the weight of the brain; hence fractures occur (figs. 11 and 12).

As is evident in this case (figs. 13, 14, 15), there are times when the disease assumes the characteristics of a hemangioma of the bone. Similar small tumors of bone have been found elsewhere in the skeletal anatomy. Horwitz[3] found one in a digit. Jaffe[4] reports the presence of osteoid-osteoma in the long bones. Studying his specimens and ours in his laboratory, both of us were impressed with the similarity in some of the microscopic pictures. His tumors are accompanied by pain. Pain has not been recorded as a symptom in otosclerosis. How often "headache" appears in the history, the clinician must know. Kelemen[5] found an osteoma in the frontal sinus which "simulated the final stage of an oto-

FIG. 11—The otosclerotic lesion may not occur at the site of the fracture line. The fracture line occurs because of the loss of support induced by the otosclerotic process. (Washington University Collection, 7010.)

FIG. 12—Fracture lines occur because the petrosa has been weakened by the decalcification of the bone. The petrosa is the support for the weight of the brain and the dome of the skull. Fractures will occur wherever the strain is too great for the remaining bone to bear; not necessarily in the area of otosclerosis. (Washington University Collection, 5178.)

sclerotic lesion." Similar osteomas have been reported in the external auditory canals of otosclerotic patients.

Nager and M. Meyer[12] at one time thought of otosclerosis as a localized form of Paget's disease. Osteitis fibrosa is now recognized as Nature's reaction to rapid decalcification of bone (fig. 16). When ankylosis of the stapedial footplate occurs in these cases, a diagnosis of otosclerosis will be made.

Gerlings and de Kleyn[2] found otosclerosis in a case of gargoylism. I have collected a case of gargoylism (dysostosis multiplex) in which there was no evidence of otosclerosis, but there were joint changes in the ossicles and porosity of the petrosa as a whole.

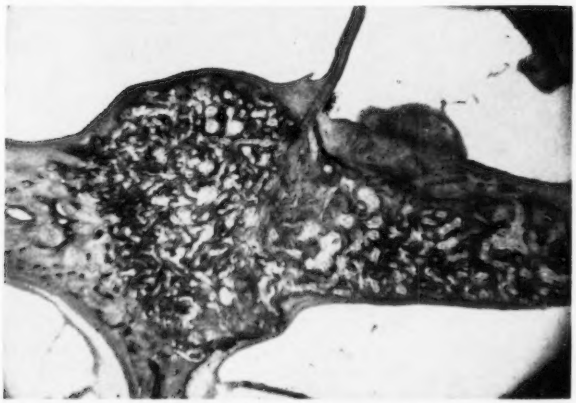

FIG. 13—Note the thickened footplate of stapes, covered by thickened mucosa containing congested vessels. Extensive ankylosis has occurred in this case with a history of deafness for nine years. White female, 23 yrs. (Dr. Lempert's case.)

FIG. 14—The oval window shown at a lower level than in the preceding photograph. Note the large tumor-like mass of bone lying between the crura of the stapes. Its origin may be seen in figure 15. Round window was normal.

Otosclerosis can also be shown to be a localized form of osteoporosis (figs. 4 and 17). Evidently, after excessive vascularization has occurred, an embolus or obliterative arteritis blocks the blood supply to the area and produces the pathologic condition observed. It is interesting to note the lesion in the internal auditory meatus where the tissue fluids have simply washed the necrotic bone away without any reaction toward repair (fig. 17).

Otosclerosis may be accompanied by increased pressure within the labyrinth, as was pointed out by M. Meyer.[10] Figures 18, 19 and 20 illustrate a case of Ménière's syndrome. The diagnosis was not clear-cut. As you see, otosclerosis is present but no clinical diagnosis was made. There is no

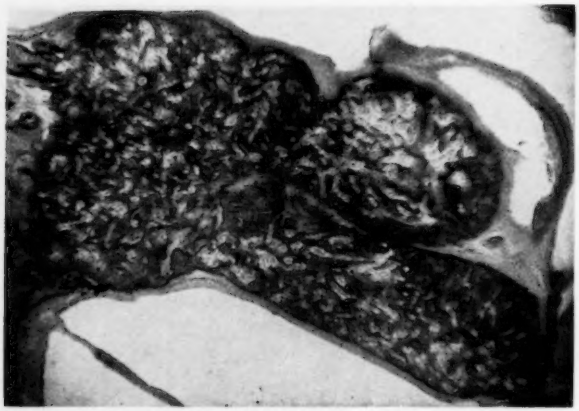

FIG. 15—The origin of the hemangiomatous tumor is seen to be the promontory wall. Congestion and stasis of vessels, fibrosis of the bone and osteoclasia were all present.

ankylosis of the stapes. Hydrops of the labyrinth is present in both ears. Also, in the vestibular ganglion of the right ear there is an area of atrophy of ganglion cells. This is found to be due to obliterative arteritis. In its end stage one cannot determine whether the lesion developed from obliterative periarteritis, as in periarteritis nodosa, or from obliterative endarteritis. The patient was a dentist and suffered from severe disorientation and dizziness. It is not impossible that similar lesions may also have occurred intracranially to obscure diagnosis further. Druss and Maybaum[1] reported periarteritis nodosa of the temporal bone in two cases showing otosclerosis and having a diagnosis of generalized periarteritis nodosa.

It is well known that otosclerosis may be found in cases of blue sclera.

Thus we see that otosclerosis may assume many forms. It has a multiple etiology. It may occur in any case with bone or calcium dyscrasia. It may arise in any case where peripheral vascular pathologic conditions exist. These may block the normal release and resorption of calcium in an area.

Peripheral vascular pathologic conditions arising from whatever cause explain the bilateral symmetry of the disease. It is well known that the same phalanx of the same digit in bilateral extremities may simultaneously be affected in peripheral vascular disease.

Peripheral vascular disease explains the decalcification process. Sluggish blood in excess numbers of capillary loops has been observed in the nail beds of patients with peripheral vascular disease. Decalcification of bone commonly occurs in the presence of stasis.

Peripheral vascular disease explains why some cases show atrophy of stria vascularis, spiral ganglion, and organ of Corti. It means that the internal auditory artery is also affected. It explains hydrops of the labyrinth in the same way. It explains why loss of word hearing is sometimes greater than the audiometer record for pure tones indicates that it should be.

Tinnitus may possibly be due to alterations in vascular channels such as the inferior tympanic artery or, indeed, others in the area.

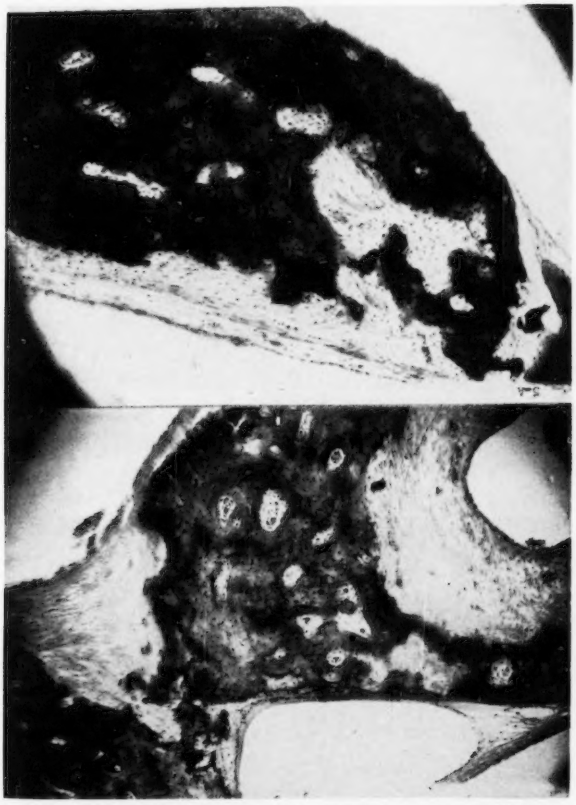

FIG. 16—Osteofibrosis and overgrowth of pathologic bone in the footplates of the right and left stapes in a bilateral case of otosclerosis. (Courtesy of Dr. Kinney.)

When ankylosis of the footplate, immobilization of the other two ossicles, or atrophy of the muscles in the middle ear due to loss of blood supply occurs one can imagine that the clinician will get these changes reflected in the audiometer record. Whether there are two types of records for involvement of the two windows, I do not know.

I predict that when a complete reconstruction of the detailed terminal blood supply of the adult petrosa is made we will find the areas of more or less terminal capillaries with little or no chance for anastomoses to be the sites of predilection for otosclerosis.

The incipient and early progressive stages of the disease and the various microscopic aspects it may assume have recently been reported in the literature by Dr. Lempert and myself. Study of his large collec-

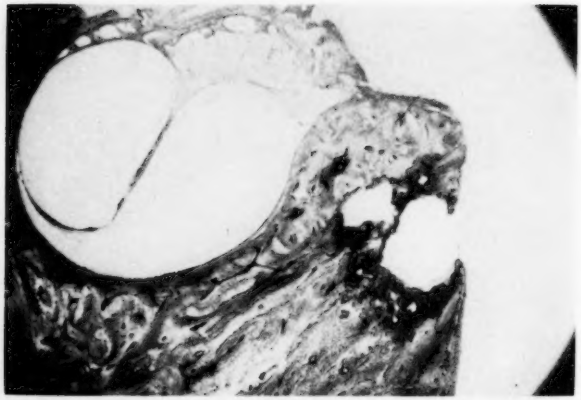

FIG. 17—Complete dissolution of bone in the internal auditory meatus in the same case in which the isolated otosclerotic area of osteoporotic type was seen along the base of the cochlea. Note the atrophy of stria vascularis, organ of Corti and spiral ganglion. (Washington University Collection, 8630.)

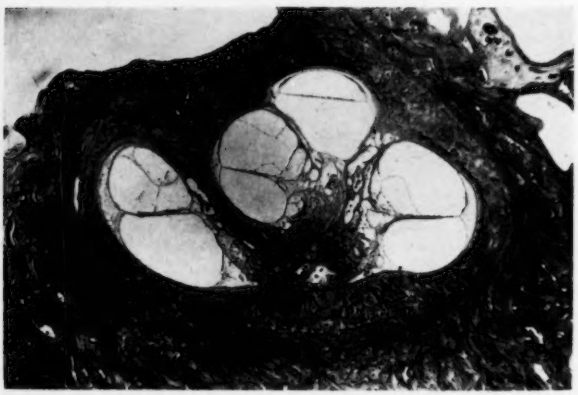

FIG. 18—A typical picture of a distorted Reissner's membrane in hydrops of the labyrinth. Adult, white male. (5178 1ft., 1052.)

tion of ossicles has led us to the hypothesis that otosclerosis has no specific etiology but that it is the result of damage to the peripheral blood supply. This might be chemical, vasomotor, or allergic. It may be trauma from vibratory phenomena. What trend the ultimate course of the disease will take depends upon the constitution of the individual patient. In some there may be a hemangioma. In others fibrosis will occur. In still others osteoporosis may develop.

FIG. 19—Distortion of membranes in the cochlea and vestibule in a case of bilateral hydrops of the labyrinth and otosclerosis. (Washington University Collection, 5178 rt.)

FIG. 20—Obliterative endarteritis in the artery supplying the vestibular ganglion. This lesion produced extensive atrophy of the ganglion, with clinical symptoms. (5178 rt.)

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# THE INFLUENCE OF SYSTEMIC AND LOCAL FACTORS ON THE DEVELOPMENT OF OTOSCLEROSIS

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INVESTIGATIONS which have been made in the search for evidence of relationship between otosclerosis and other systemic diseases have so far yielded little positive information as to its etiology. Attention has been directed to various diseases of glands of internal secretion, hormone imbalance, vitamin deficiencies and metabolic disturbances, but laboratory investigations have so far revealed no specific connection.

The presence of a hereditary predisposition to otosclerosis has been demonstrated in as high as 50 per cent of some large series of clinical cases. Although the disease is known to exist without clinical symptoms in a large percentage of people and the application of Mendelian laws is therefore impractical, the existence of a hereditary factor seems definite.

Clinical observation has provided some evidence that certain constitutional factors may exert some influence on the progress of the disease, perhaps also on its development. Certain constitutional states may furnish the environmental influence necessary to activate the disease. A review of the available information regarding constitutional and local factors which may influence the disease is therefore in order in the search for possible leads for further investigation.

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Histopathologic studies have so far given basic information about the development and structure of the labyrinthine capsule, and the changes which occur in it as a part of the various diseases affecting bone. These have added greatly to our understanding of the otosclerosis problem, but more definite information as to etiologic factors has been lacking. The special structure of the labyrinthine capsule is well known and the development of the three layers has been accurately followed.[1]

The lack of necessity for further growth of the labyrinthine spaces after fetal life has made possible the peculiar structure of the middle or enchondral layer of the capsule, in which the primary bone with its enclosed spicules of calcified cartilage persists throughout life.

The endosteal and enchondral or endochondral layers have an unusually dense character and show a special resistance to most disease processes which readily affect the outer periosteal layer. The enchondral layer is also known to exhibit comparatively little osteogenetic activity following fracture. Healing of the fracture takes place mainly from the endosteal and periosteal surfaces.

The periosteal layer of bone continues to be added to during growth of the base of the skull, thereby increasing the over-all dimensions of the pyramid. Marrow spaces may persist in this layer

in areas surrounding the capsule as well as in the apical part of the pyramid. Pneumatization also is limited to the periosteal layer.

### EFFECT OF VARIOUS DISEASES OF THE BONY SKELETON ON THE LABYRINTHINE CAPSULE

There are a number of extensive reports on the histopathologic changes in the petrous pyramid in the presence of various diseases affecting bone. Investigations by Siebenmann, Manasse, Wittmaack, Nager, Mayer, Meyer, Brunner, Weber, Wilson and Anson and many others have shown the extent to which the different layers of the capsule tend to be affected by diseases affecting the skeleton as a whole. These reports are included in the resume of the literature by the Central Bureau of Research of the American Otological Society, Inc., in four volumes entitled "Otosclerosis."[2]

Rickets has been shown to affect mainly periosteal bone of the pyramid and to have no relation to otosclerosis. The changes in senile osteoporosis and osteomalacia have been mainly in periosteal bone; the enchondral layer has shown little evidence of absorption. The endemic deafness of the Alpine regions associated with cretinism, bone deformities and dwarfism is related to the deposition of new periosteal bone to the promontory with narrowing of the window niches, interference with and sometimes malformations of the ossicles.

Albers-Schönberg disease, also known as marble bones or osteosclerosis, has been characterized by a deposition of enormous amounts of dense periosteal bone. The labyrinthine spaces have been found free from encroachment and the sensory structures not involved. The deposition of extremely thick new periosteal bone has resulted in extensive changes affecting middle ear spaces and the course of nerves through the periosteal layer, but the enchondral and endosteal layers are clearly recognizable and have not been replaced.

Chondrodystrophy has not been associated with any apparent tendency to otosclerosis in the case of those who have reached adult life. The same alterations in the ossification zones of the pyramid have been observed as are known to occur in extremities, leading to dwarfism. In Paget's disease or osteitis deformans the enchondral layer does not escape the disease process. In those cases where the temporal bone is involved the destruction and new formation of bone starts from the periosteal layer but involves all layers eventually. The type of deafness may be conduction in early stages due to impedance at the stapedo-vestibular joint but a progressive nerve deafness is characteristic. Sometimes a sudden episode of deafness and dizziness has occurred in the late stages. The histopathologic alterations in Paget's disease are similar in detail to those seen in some areas of active otosclerosis. The distribution and rate of progress however is quite different. The etiology of Paget's disease is also unknown and nothing has been found as yet that will appreciably influence the progress of the disease.

The type of osteodystrophy seen in the generalized osteitis fibrosa of von Recklinghausen, with tumors of the parathyroid gland, has shown resemblance to some areas of an active otosclerotic nodule. Nager and Meyer, and Weber considered otosclerosis to be a local osteodystrophy.

### BLUE SCLERA, FRAGILE BONES AND OTOSCLEROSIS

The frequent association of blue sclera, fragile bones and otosclerosis and the hereditary tendency of this syndrome (Van der Hoeve-de Kleyn syndrome) has been of especial interest.

The familial tendency has been studied in many family trees for three and four generations.

According to Fowler[3] the incidence of blue sclera in otosclerosis was found to be 69 per cent, and the incidence of otosclerosis in those with marked blueness of the scleras was 50 per cent.

The incidence of otosclerosis in osteogenesis imperfecta cannot be estimated since the deafness appears only in the second or third decades, whereas the majority of children born with osteogenesis imperfecta do not survive to adult age.

Not all children with blue sclera in affected families have fragile bones, but in such families the existence of the triad in those who have reached adult life is frequent.

Examination has shown that the periosteal layer of the capsule has been mainly affected. Upon doing the fenestration operation on such a case the bony trabecula were found to have a strikingly fine and delicate character with the bony labyrinthine capsule of apparently normal hardness but thinner than usual.

The occurrence of this syndrome has been of especial interest from the standpoint of otosclerosis. However, little is known about the etiology of osteogenesis imperfecta or of blue sclera. The nature of the relationship to otosclerosis is not definite although both diseases have shown a hereditary tendency.

### REACTION OF THE LABYRINTHINE CAPSULE TO LOCAL FACTORS SUCH AS INFECTION AND TUMOR

Inflammatory disease which enters the pyramid by way of the air spaces affects mainly the periosteal bone. The enchondral and endosteal layers offer great resistance to invasion, but in the event of the process becoming walled off in a group of air cells or in marrow spaces the enchondral layer as well as the endosteal layer may eventually break down. Direct resorption of all layers may then occur along the surface and along vascular spaces, or sequestrums may form, presumably as a result of obliteration of blood supply.

A suppurative process within the labyrinth may invade all layers of the bony capsule. The greater density of the endosteal and enchondral layers, however, provides for greater resistance to invasion by infection on the part of these layers than in the case of the periosteal layer. The latter probably owes its vulnerability to the presence of air spaces, vascular and marrow spaces.

Similarly, in the presence of tumor the enchondral and endosteal layers resist invasion and absorption more effectively than the periosteal layer. This may be accounted for, in part at least, by the absence of air and marrow spaces and the relative avascularity of the middle and inner layers of the capsule.

### CONSTITUTIONAL FACTORS

There has been no conclusive evidence from clinical observation that disturbances of internal secretion or hormones or vitamin imbalance have been related to otosclerosis. The clinical impression exists, however, that pregnancy has some tendency to activate the disease, and also that prolonged illness may have a similar influence. The statistics presented by Guild[4] appear to indicate a higher frequency of otosclerosis in persons who have died between the ages of 30 and 49 than in the corresponding period over the age of 49. The significance is not readily apparent, but the question arises as to whether the incidence in normal healthy people in this age period would be similar to that in the same classification in the older age group.

The incidence of otosclerosis found on autopsy may depend in part upon

the material available; for example, the type of institution, the predominant age group, the incidence of intracranial disease, and the special interests of the collector. Large collections from normal healthy adults may show a lower incidence.

Available statistical reports seem to indicate an approximate incidence of around 10 per cent in autopsied material from white adults.

In histologic examination of the author's collection of 22 temporal bones showing definite otosclerosis, the question has arisen whether some of the otosclerotic nodules found could have originated during the terminal illness and, if so, whether that illness was a necessary environmental factor in their etiology.

The collection contains four bones which were obtained because the person was known to have otosclerosis; all the other examples were found on routine postmortem examination. The majority of these, however, came from patients with intracranial disease such as tumor, osteomyelitis and meningitis.

Three cases (six temporal bones) show what may be described as a very early active stage of the disease. Due to the occurrence of these cases, the question has been raised whether the prolonged terminal illness may have been the environmental factor which activated the otosclerosis in an individual with a hereditary tendency toward development of the condition.

## CASE REPORTS

*Case 1*

E. A. Female, 9 years of age. Death occurred from an intracranial malignant neoplasm which was known to have existed for about one year.

Examination of the temporal bones showed essentially normal middle and inner ears, but in the labyrinth capsule, just in front of the oval window on each side, was a small well demarcated area of pathologic bone which exhibited a very early active stage of otosclerosis. In some areas osteoclasts were visible bordering both on otosclerotic bone and upon the primary bone of the enchondral layer. Rows of osteoblasts were also visible in some of the enlarged marrow spaces. Blood vessels were prominent in this fibrotic type of marrow. In one temporal bone, extension could be observed along a vascular space at the margin of the otosclerotic nodule. The nodules were similar in size and in their apparent activity. The periosteal and enchondral layers were both involved. The calcified cartilage along the oval window and fissula did not appear to be primarily affected, although it was involved to some extent.

*Case 2*

L. J. Female, age 19. Death occurred from meningeal sarcoma which had invaded both internal auditory meatuses. The middle ears, as well as the labyrinthine spaces, were essentially normal although the tumor tissue extended in to the limits of the meninges on one side.

In the area of predilection in front of the oval window a relatively small focus of otosclerosis was present with signs of active bone destruction, many marrow spaces containing fibrous marrow and dilated blood vessels. Extension along vascular spaces was evident in several areas in each focus. All layers of the capsule were involved and there was considerable thickening of the annular ligament, but no absorption of the calcified cartilage which forms the margin of the stapes footplate was present.

*Case 3*

T. K. Male, age 30. Death resulted from meningitis secondary to osteomyelitis of the sphenoid, complicating scarlet fever. Both temporal bones showed evidence of inflammatory reaction in the middle ears without frank suppuration, and an early stage of extension of the meningitis to the labyrinth.

The labyrinthine capsule was normal in all areas except at the outer margin of the attachment of the round window membrane to the bone. Here a very small localized area was present bilaterally showing active resorption of bone, fibrotic and highly vascular bone marrow and laying down of new bone. The size and activity of the areas were such as to indicate a probable recent beginning of the process.

These 3 cases present early stages of otosclerosis, two at the area of predilection in front of the oval window and

one at the next most common site, the attachment of the round window membrane at its lateral margin.

The stage of activity evident on histologic examination and the minute size of the nodules indicate that they might well have taken origin within a period of weeks and thus may have represented the effect of a prolonged terminal illness upon a subject already possessing a hereditary tendency toward otosclerosis.

*Case* 4

Adult male. Death resulted from pernicious anemia. The left temporal bone was normal. Pneumatization was extensive, the inner and middle ears and the bony capsule were normal. The right temporal bone showed almost complete absence of pneumatization of the mastoid with a distorted and damaged tympanic membrane adherent to the medial wall of the middle ear, the result of former suppurative disease which had healed.

The inner ear was normal.

The labyrinthine capsule of this ear contained a well demarcated nodule of otosclerosis in the area in front of the stapes. Signs of activity were much less apparent than in the cases described above and sclerosis was more advanced. There was no evidence of involvement of the stapes.

The association of otosclerosis with old inflammatory disease and absence of pneumatization, with the opposite ear completely normal and well pneumatized, supports the opinion often held by former observers that a local pathologic process such as chronic inflammation might provide the necessary factor for activation of otosclerosis in the presence of a hereditary disposition.

These 4 cases seem to give evidence to support the belief that some environmental factor, either through a local effect or a constitutional influence may play an important part in starting the disease process in one already possessing a hereditary tendency toward its development.

## EXPERIMENTAL EVIDENCE

Otosclerosis has never been observed in lower animals.

Efforts to produce an experimental lesion resembling the disease have so far failed. Experiments reported in the literature have included the effect of dietary restrictions, excessive use of certain hormones, and certain drugs and chemicals.

The labyrinth of the monkey bears the greatest resemblance to the human labyrinthine capsule. In it the enchondral layer contains cartilaginous remnants and even some evidence of the fissula fenestra anterior may be found. Young rabbits exposed to a diet deficient in vitamin A have shown extensive development of new bone, which was superimposed mainly on dural surfaces of the skull, resulting in constriction of nerve channels and pinching of nerves.[6,7,8] The enchondral and endosteal layers of the capsule showed no significant changes, probably because growth of the labyrinthine spaces had been completed.

Injection of large doses of parathormone has produced a type of osteodystrophia fibrosa in young dogs and has been reported to cause changes in the labyrinthine capsule similar to otosclerosis.[9]

Injection of parathormone for a period of four months in young monkeys failed to produce any definite change in the labyrinthine capsule.[10]

Electrocoagulation of the labyrinthine capsule in experiments on the monkey has been observed by the author to be followed by active resorption of the affected bone and replacement by new bone. The enchondral layer is affected as actively as the periosteal layer. The resorption takes place along vascular channels. These become dilated as bone is absorbed from the walls, and filled with fibrous marrow. As the old

bone is removed, new bone is eventually deposited to fill the defect.

SUMMARY

The attempt to link up otosclerosis with other general constitutional disorders has so far demonstrated no definite relationship with them either by clinical or experimental investigation.

Clinical observation suggests the existence of a hereditary predisposition.

The possible environmental influence of prolonged constitutional disturbances and of pregnancy is also suggested by clinical observation. In addition, chronic inflammatory changes in the ear may act sometimes as an environmental factor necessary for production of the disease in the presence of a hereditary predisposition.

The histopathologic appearance of an otosclerotic nodule in some areas indicates a resemblance to osteitis deformans or Paget's disease but differs greatly from the latter in its extent, rate of development and its hereditary tendency.

In neither condition is the etiology known nor is any treatment known to have a favorable effect.

A definite relationship is clinically evident between blue sclera, fragilitas ossium or osteogenesis imperfecta and otosclerosis. The existence of some common hereditary constitutional factor is suggested to account for the predisposition to any one or any combination of these conditions.

The endosteal and enchondral layers of the capsule are resistant to most general bone diseases. Osteitis deformans or Paget's disease and otosclerosis are exceptions.

These layers exhibit resistance to osteolytic processes. Infections and tumors invade and destroy the periosteal layer more readily, probably because of its air cell content and marrow spaces. Infection which is blocked off in deeper parts of the temporal bone frequently invades the enchondral layer and sequestration of all layers sometimes occurs.

Death of the enchondral layer may result from electrocoagulation and is followed by active absorption along vascular channels with ultimate removal and replacement by new bone.

While it has been possible experimentally to produce alterations in the bones of the skeleton and the outer layer of the labyrinthine capsule by various means, the inner layers of the capsule have shown great resistance to change.

Further basic research into the biologic processes involved in normal growth and metabolism of cartilage and bone would seem indicated as a preliminary to the study of such bone diseases as Paget's, osteogenesis imperfecta, and otosclerosis.

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